address the enablement rejection, discussed below. Thus, claims 16-20 remain pending and at issue.

Request for Interview

Applicants request a telephonic interview with the Examiner, if, after reviewing the instant Amendment, he finds that there remain issues which are an impediment to allowance. The Examiner is invited to telephone the undersigned at his earliest convenience to arrange for such an interview.

Rejection Under 35 U.S.C. § 112, First Paragraph

The Examiner has maintained the rejection of claims 16-20 under 35 U.S.C. § 112, first paragraph. The Examiner contends that while claims 16-20 are enabling for small molecules of formula I, he maintains that the instant specification does not reasonably enable all small molecules.

Without conceding the propriety of the rejection and strictly in the interests of advancing the prosecution of this application, Applicants have amended the claims to refer to a method of treatment comprising the administration of a carboxylic acid hydroxamide derivative having the claimed molecular weight and biological activity. Support for this amendment to the claims can be found in the instant specification, *inter alia*, at page 5, lines 3-23, page 9, line 14, to page 13, line 18, and page 51, line 8, to page 63, line 12.

Nevertheless, if the Examiner maintains that the specification is not enabling for all carboxylic acid hydroxamide derivatives, Applicants offer the following traversal. Preliminarily, Applicants previous response, filed December 27, 2001, is incorporated herein by reference in its entirety.

Applicants respectfully submit that the specification as filed complies with the enablement requirement. Section 112 requires that a specification shall contain a written description of the manner and process of making and using the invention in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same. In accordance with the statute, the specification of the instant application fully supports and enables the pending claims. The test of enablement is whether one skilled in the art could make or use the invention relying on the disclosure in the patent coupled with information known in the art without undue experimentation. *U.S. v. Telectronics, Inc.* 8 USPQ2d 1217, 1223 (Fed. Cir. 1988); M.P.E.P. § 2164.01. Applicants also submits that statements in the specification are to be accepted as presumptively true. *In re Brana*, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995).

Applicants have submitted an enabling disclosure including the use of ex mplified carboxylic acid hydroxamide derivatives that are believed to be the best mode, *e.g.*, see pages

65-82 of the specification as originally filed. Applicants have also described multiple schemes of preparation and starting materials that could be used by one skilled in the art to prepare the small molecules, *e.g.*, see pages 22-51 of the specification, Schemes 1-7 and their descriptions. Applicants have stated throughout the specification that their invention is useful for treating a medical condition of the type that is characterized by the destruction of articular cartilage in a mammalian subject. See for example the specification page 13, lines 19-30. Applicants have also described several aggrecanase and TACE assays (pages 51-55), which demonstrate the utility of the claimed compounds. Applicants have also provided the exemplified activity data of the claimed compounds against collagenase-1 (see page 51), against collagenase-3 (see page 52), against aggrecanase (see page 53), and against TACE (see page 55). Applicants have further provided comparative data in Table 2 on pages 56-63 of the specification, which shows activities data for many preferred hydroxamic acids, against aggrecanase, MMP-13, MMP-1 and TACE. Applicants have also provided a detailed description of methods for dosing and formulating the compounds of the invention, see pages 63-64. The Examiner has not challenged Applicant's disclosure on any of these points. Instead, the Examiner has, without any factually supported evidence, concluded that Applicants' broad claims lack sufficient supporting description. Such factually unsupported evidence argued in the absence of the specification disclosure and cited literature is contrary to Patent Office standards and Applicant objects to such improper line of analysis, see M.P.E.P. 2164.01(a), which states:

> It is improper to conclude that a disclosure is not enabling based on analysis of only one of the above factors while ignoring one or more of the others. The Examiner's analysis must consider all the evidence related to each of these factors, and any conclusions of non-enablement must be based on the evidence as a whole. 858 F.2d at 737, 740, 8 U.S.P.Q.2d at 1404, 1407.

The Examiner's obligation is clearly to ground his reasoning in factual evidence, see M.P.E.P. 2164.04, which states:

> As stated by the court, "It is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure."... This can be done by making specific findings of facts, supported by the evidence, and then drawing conclusions based on these findings of fact (emphasis added).

In responding to Applicants' comments regarding the Examiner's analysis of *In re Fisher*, the Examiner concluded that "[i]t is the breadth and open-ended nature of Applicants' compound structural limitation to which the Examiner objects" (Office Action at 5), seemingly relying the *Fisher* court's conclusion that claims that do not "bear a reasonable correlation to"

the scope of the disclosure violate Section 112, first paragraph. However, as amended, the claims are now commensurate in scope with the disclosure. They are not open-ended and now contain a significant structural limitation, i.e., the invention being limited to the administration of carboxylic acid hydroxamide derivatives, which allows the skilled artisan to divine the metes and bounds of the invention.

Further, Applicants reiterate that unlike the claims in the *Fisher* case which call for a level of potency which is significantly higher than that achieved in prior art preparations of ACTH, the present claims call for a carboxylic acid hydroxamide having a molecular weight of under 2000 grams/mole, which are obtainable from applicants' teachings plus ordinary skill. In contrast to the low level of ordinary skill in the preparations of ACTH art applicable to Fisher, the ordinary skill of the preparation and use of variety of carboxylic acid hydroxamides for treating a medical condition of the type that is characterized by the destruction of articular cartilage is high. In this regard, Applicants once again call the following U.S. Patents to the Examiner's attention, which are directed to carboxylic acid hydroxamide derivatives that are useful for treating a medical condition of the type that is characterized by the destruction of articular cartilage:

- U.S. Patent No. 6,326,516, entitled "Acetylenic β-sulfonamido and phosphinic acid amide hydroxamic acid TACE inhibitors";
- U.S. Patent No. 6,313,123, entitled "Acetylenic sulfonamide thiol TACE inhibitors;
- U.S. Patent No. 6,277,885, entitled "Acetylenic aryl sulfonamide and phosphinic acid amide hydroxamic acid TACE inhibitors;
- U.S. Patent No. 6,225,314, entitled "Inhibition of matrix metalloproteases by substituted biaryl oxobutyric acids;
- U.S. Patent No. 6,225,311, entitled "Acetylenic α-amino acid-based sulfonamide hydroxamic acid TACE inhibitors;
- U.S. Patent No. 6,200,996, entitled "Heteroaryl acetylenic sulfonamide and phosphinic acid amide hydroxamic acid TACE inhibitors;
- U.S. Patent No. 6,197,795, entitled "Preparation and use of ortho-sulfonamido heteroaryl hydroxamic acids as matrix metalloproteinase and TACE inhibitors;
- U.S. Patent No. 6,162,821, entitled "Preparation and use of ortho-sulfonamide heteroaryl hydroxamic acids as matrix metalloproteinase and TACE inhibitors;
- U.S. Patent No. 6,162,814, entitled "Preparation and use of ortho-sulfonamido heteroaryl hydroxamic acids as matrix metalloproteinase and TACE inhibitors;
- U.S. Patent No. 5,977,408, entitled "Preparation and use of β-sulfonamido hydroxamic acids as matrix metalloproteinase and TACE inhibitors;
- U.S. Patent No. 5,968,795, entitled "Biaryl acetylenes as inhibitors of matrix metalloproteases;
- U.S. Patent No. 5,962,481, entitled "Preparation and use of ortho-sulfonamido heteroaryl hydroxamic acids as matrix metalloproteinase and TACE inhibitors;
- U.S. Patent No. 5,932,763, entitled "Inhibition of matrix metalloproteases by 2-(.omega.-aroalkyl)-4-biaryl-4-oxobutyric acids;
- U.S. Patent No. 5,929,097, entitled "Preparation and use of ortho-sulfonamido aryl hydroxamic acids as matrix metalloproteinase and TACE inhibitors;
- U.S. Patent No. 5,925,637, entitled "Inhibition of matrix metalloproteases by substituted biaryl oxobutyric acids;
- U.S. Patent No. 5,804,581, entitled "Inhibition of matrix metalloproteases by substituted phenalkyl compounds; and

- U.S. Patent No. 5,677,282, entitled "Amino acid amides of 1,3,4-thiadiazoles as matrix metalloproteinase.

Thus, Applicants respectfully submit that based on Applicants' teachings in addition to the high ordinary skill level described above, carboxylic acid hydroxamide derivatives having a molecular weight of under 2000 grams/mole are obtainable. Therefore the present claims are enabled.

Furthermore, in responding to Applicants' comments on In re Strahilevitz, the Examiner made the following observations:

> *In re Strahilevitz* . . . concerned use of a hapten removing device' to achieve a therapeutic goal. Applicants are claiming use of [a] compound for achieving a therapeutic goal. The issue of the structure of the device was not directly considered by the court but it did note that in finding 3] that dialysis membranes were described in the specification and the court stated the 'invention resides in combining the known prior art techniques of hemodialysis or hemoperfusion . . .'. One can infer the court believed the '. . . hapten-removing device' is a machine used for hemodialysis or hemoperfusion and well known in the art. In addition the patent which arose from *In re Strahilevitz* . . . contains in claim 1 . . . a specific description of the device. Thus, *In re Strahilevitz* . . . is not on point technically because this was a mechanical not a chemical issue and not on point legally because the mechanical apparatus was claimed in terms more narrow than its weight and intended function, which is what Applicants are doing. Office Action at 3-4.

However, as amended, Applicants' claims do contain a specific description of the device, by structure and function. Further, based on the above legal precedents, the numerous examples of carboxylic acid hydroxamide derivatives provided by Applicants, the breadth and depth of the level of the ordinary skill, and the copious number of hydroxamide derivatives in the art related to those in the present application, Applicants respectfully submit that they have put the public in possession of the claimed invention. Applicants have therefore provided more than sufficient basis for one of ordinary skill in the art to practice the teaching of the specification.

Rejection Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 16-20 as indefinite to particularly point out and distinctly claim the subject matter that Applicants regard as the invention. In particular, the Examiner objects to the term "small molecule". As discussed above, Applicants have amended the claims to refer to carboxylic acid hydroxamide derivatives in order to more specifically define the class of compounds sought to be protected by the claimed method of treatment. In particular, as amended, claims 16-20 refer to "a carboxylic acid hydroxamide derivative with a molecular weight of under 2000 grams/mole, wherein the small molecule exhibits an aggrecanase IC_{50} of less than about 20 nM, said aggrecanase IC_{50} measured by an aggrecanase chondrocyte assay." Applicants respectfully submit that the scope of the claim as written is very definite

because the small molecule is defined both by its structural characteristics, i.e., carboxylic acid hydroxamide derivatives, molecular weight (under 2000 grams/mole) and its feature (an aggrecanase IC_{50} of less than about 20 nM).

For at least these reasons, Applicants respectfully submit that claims 16-20 satisfy 35 U.S.C. §112, second paragraph, and the rejection should be withdrawn.

Rejection Under 35 U.S.C. § 102(e)

The Examiner has rejected claims 16-20 under 35 U.S.C. §102(e) as being anticipated by Robinson (U.S. Patent No. 6,114,361); Reiter (U.S. Patent No. 6,087,392); and Duan (U.S. Patent No. 6,057,336).

Applicants respectfully traverse the Examiner's rejections on the grounds that the present claims 16-20 call for a carboxylic acid hydroxamide derivative that exhibits an aggrecanase IC_{50} of less than about 20 nM. This requirement is not present anywhere in any of the above references cited by the Examiner. To anticipate a claim, a single source must contain all of the elements of the claim. See *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379, 231 U.S.P.Q. 81, 90 (Fed. Cir. 1986); *Atlas Powder Co. v. E.I. du Pont De Nemours & Co.*, 750 F.2d 1569, 1574, 224 U.S.P.Q. 409, 411 (Fed. Cir. 1984); *In re Marshall*, 578 F.2d 301, 304, 198 U.S.P.Q. 344, 346 (C.C.P.A. 1978). Missing elements may not be supplied by the knowledge of one skilled on the art or the disclosure of another reference. See *Structural Rubber Prods. Co. v. Park Rubber Co.*, 749 F.2d 707, 716, 223 U.S.P.Q. 1264, 1271 (Fed. Cir. 1984). However, the prior art reference is not limited to its examples or its claims; the entire reference may be reviewed for an anticipatory disclosure. See *Paleckal v. Resconi*, 2000 Pat. App. LEXIS 1, *54 (Bd. Pat. App. & Int. 2000)(non-precedential) citing *In re Mills*, 470 F.2d 649, 651, 176 U.S.P.Q. 196, 198 (C.C.P.A. 1972).

The Examiner appears to be relying on the inherent characteristics of the prior art compounds to substantiate the instant anticipation rejection. In particular, the Examiner concedes that the claimed potencies of the compounds recited in the present claims are not found in the prior art. Nevertheless, the Examiner concludes that "[f]or all the Examiner knows, the compounds taught in Robinson . . . , Reiter . . . , and Duan . . . do have the required potency" (Office Action at 8). However, as articulated above, to anticipate a claim, a single source must contain all of the elements of the claim, i.e., in this case, each of the cited references must disclose a carboxylic acid hydroxamide derivative having a molecular weight of less than 2000 g/mole, and an aggrecanase IC_{50} of less than about 20 nM. The Examiner has failed to show that the cited prior art have all of the features, which is what is required under Section 102.

In this regard, the Examiner is respectfully invited to review MPEP § 2112, which provides an explanation of the requirements of a rejection based on inherency, and in particular, the Examiner's burden of proof in establishing such a rejection. The fact that a certain result or

characteristic *may* occur or be present in the prior art is not sufficient to stablish the inherency of that r sult or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534 (Fed. Cir. 1993); *In re Oelrich*, 666 F.2d 578, 581-82 (CCPA 1981). Moreover, it is well established that in order to establish anticipation by inherency the Examiner must provide extrinsic evidence to bolster the primary reference's teachings and

> the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' *In re Robertson*, 169 F.3d 743 (Fed. Cir. 1999).

In relying on inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art. *Ex parte Levy*, 17 USPQ2d 1461 (BPAI 1990). The Examiner has not provided any reasonable basis to conclude that the cited prior art compounds would have the properties of the compounds of the present invention. Rather, he appears to rely on nothing more than assumption, probabilities or possibilities, which is a legally insufficient basis for an anticipation rejection. If he is aware of any reference teachings that would support the anticipation rejection he is invited to disclose them on the record so that Applicants may comment on them. In the absence of such extrinsic evidence, the instant rejection is untenable and should be withdrawn.

Conclusion

In light of the above arguments, legal precedents, and claim amendments, Applicants submit that the claims are in condition for allowance and such action is earnestly solicited. If after careful review of this Amendment, the Examiner maintains that there are issues that remain an impediment to allowance, he is invited to contact the undersigned in order to discuss such issues and expedite prosecution of this application.

Respectfully submitted,

Date: August 19, 2002

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